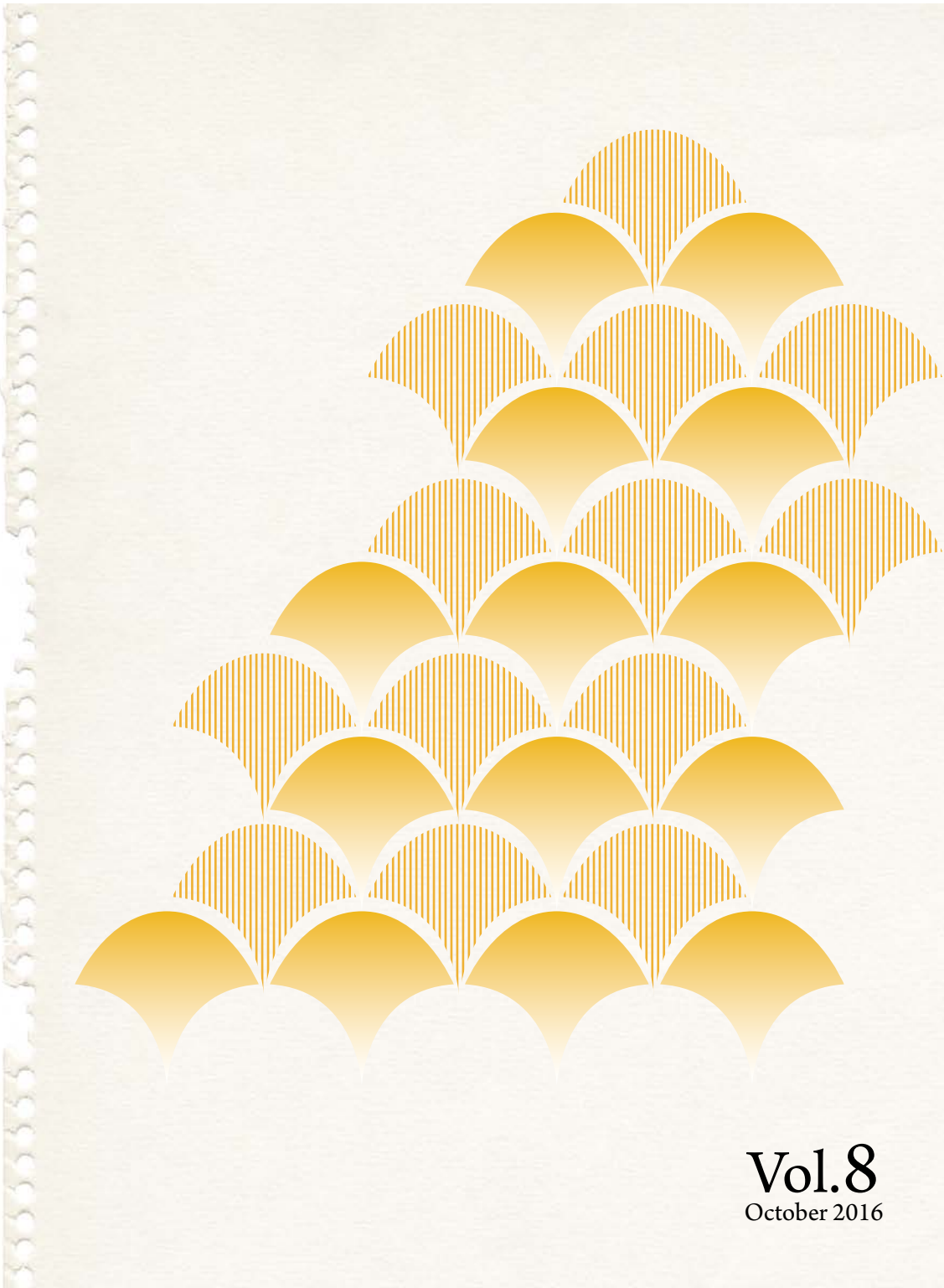
CiRA Reporter

Center for iPS Cell Research and Application,
Kyoto University



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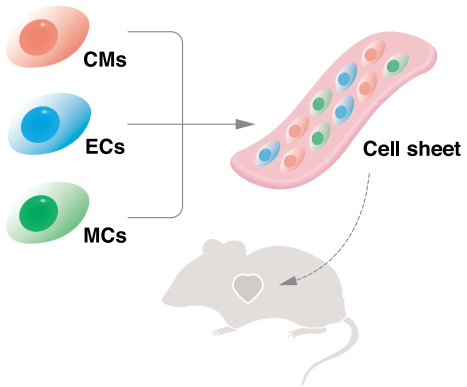
Transplantation of non-cardiomyocytes gives best recovery for heart dysfunction

The Jun Yamashita lab shows the importance of vascular cells for optimal cell therapy in heart.

Regenerative medicine for heart failure has primarily depended on replacing the lost cardiomyocytes. However, this alone rarely achieves sufficient recovery, even though cardiomyocytes are responsible for heart function. "A mix of cardiomyocytes and non-cardiomyocytes gives the best result," says CiRA Professor Jun Yamashita. As experts on iPS cell differentiation to cardiac cells, the Yamashita team partnered with pediatric cardiologist Bradley B. Keller and his group at the University of Louisville, Kentucky, who are experts on the engineering of cardiac tissues. The collaboration has recently led to a new report in *Scientific Reports* that shows how transplants of human iPS cells differentiated into three cell types, cardiomyocytes, endothelial cells (ECs) and vascular mural cells (MCs), cause good recovery in rats suffering from myocardial infarctions. "These are important preliminary experiments for clinical work," says first author Hidetoshi Masumoto, a cardiovascular surgeon and specially-appointed assistant professor at CiRA who has spent the last two years in the Keller lab.

iPS cells can make a large number of cardiomyocytes compared to other sources, but with a drawback; the resulting cardiomyocytes are generally immature compared with cells in the host heart, leading to suboptimal recovery. The study shows that by adding ECs and MCs into the transplanted tissue, cardiac function is significantly improved. This improvement was attributed to structural gains in the transplant, including better electromechanical capacity, stiffness and geometry. Successful heart function requires synchronicity in all cells constituting the heart. To achieve this synchronicity, the cells must be aligned properly so that when one cell is activated, neighbouring cells are subsequently activated or deactivated appropriately. Transplants that included ECs and MCs showed better alignment in the heart, resulting in clearly visible sarcomeres and better structural maturation, which facilitated blood flow from the host heart to the transplant. Masumoto surmised that this effect is due to genetic changes. "We found that MCs promoted the expression of genes responsible for maturation," he said. Further study of these genes is expected to reveal key molecular pathways for maximal heart recovery.



Cardiac tissue comprised of cardiomyocytes, endothelial cells and vascular mural cells had the best therapeutic effect in rats.

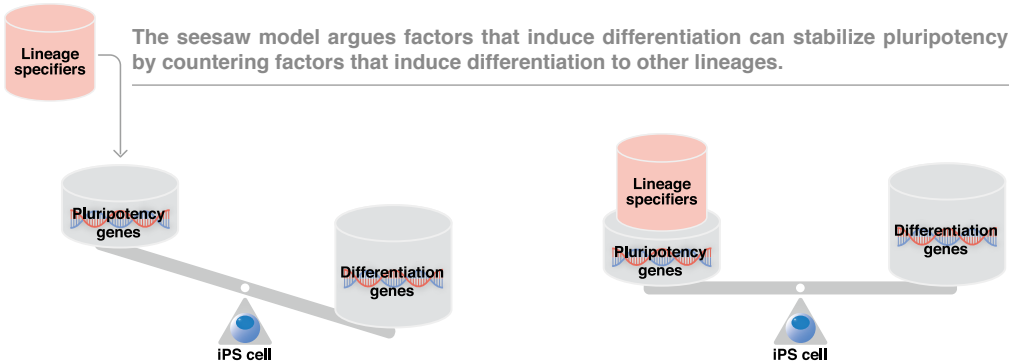
The two groups are now considering animals larger than rats and with hearts whose function more closely resemble human heart. "We want to determine the right mix of cells for best therapeutic outcomes," said Yamashita.

Reference

Masumoto H, Nakane T, Tinney JP et al. (2016) The myocardial regenerative potential of three-dimensional engineered cardiac tissues composed of multiple human iPS cell-derived cardiovascular cell lineages. *Scientific Reports* 6:29933

Differentiation promotes pluripotency

The Keisuke Okita lab shows genes that promote differentiation can be used to induce pluripotency.



Genes highly expressed in ES cells are thought to be associated with pluripotency. Accordingly, when scientists reprogram cells to iPS cells, they normally target the same genes. Yet the reprogramming efficiency is frustratingly low. CiRA scientist Tatsuya Yamakawa believes one reason is that limiting the genes to those of ES cells ignores a much larger population that could aid in the reprogramming. "I think the factors in reprogramming and pluripotency maintenance are different," he said.

The reason is the seesaw model. "The seesaw model suggests lineage specifiers could be used for cell reprogramming," explains CiRA Junior Associate Professor Keisuke Okita. Lineage specifiers are genes that promote cell differentiation, which one would intuitively expect to hinder cell reprogramming. Yamakawa and Okita, however, reasoned that expressing specifiers for one lineage could balance the expression of specifiers for another lineage, like a seesaw, thus keeping the cell in a pluripotent state. To prove this theory, the group investigated over 2000 genes, an exhaustive number, to find non-pluripotency genes that could contribute to the reprogramming. One reason most researchers do not consider differentiation genes is that the analysis is simply too demanding, but Yamakawa claimed that equipment at CiRA made the analysis more manageable. After compiling a list of candidates the lab settled on two, HHEX and HLX. "HHEX and HLX are well studied in differentiation," said Yamakawa. "I thought it would be interesting for further analysis." Indeed, the researchers found that activating either gene could increase the reprogramming efficiency by a magnitude. Interestingly, the two genes had an inclination to initiate reprogramming, but to also antagonize the maintenance, suggesting that they should only be activated for a transient period.

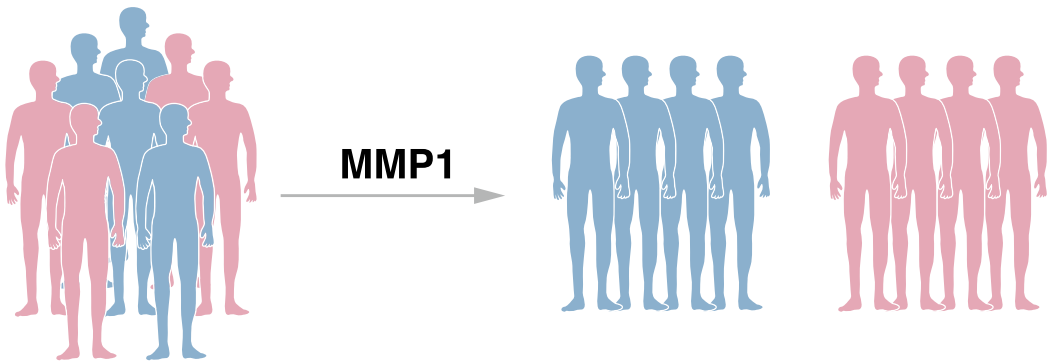
Along with running his own lab at CiRA, Okita is heavily involved in CiRA's grander aim of building a clinical-grade iPS cell bank for patient care. He expects these findings to assist in this project and that the large-scale gene analysis will help him find other candidates. "We are looking for genes that can improve the reprogramming process to make better iPS cells."

Reference

Yamakawa T, Sato Y, Matsumura Y et al. (2016) Screening of Human cDNA Library Reveals Two Differentiation-related Genes, HHEX and HLX, as Promoters of Early Phase Reprogramming Toward Pluripotency. *Stem Cells* DOI: 10.1002/stem.2436

Risk of aneurysms in kidney disease

The Kenji Osafune lab uses iPS cells to find a new marker for the risk of aneurysms that occur in kidney disease.



Doctors are unable to differentiate which AKPKD patients have a high risk for aneurysms. A new iPS cell model indicates MMP1 could be used to identify these patients.

Cystic fibrosis and sickle cell anemia are well known monogenic diseases (diseases caused by a single defective gene), but the most common is one much harder to run off the tongue, autosomal dominant polycystic kidney disease (ADPKD). ADPKD is caused by a single mutation in one of two genes, and estimates have millions of people suffering from the disease. ADPKD is marked by the formation of cysts in the kidneys that in many cases leads to severe renal failure and requires dialysis or transplantation. Because it is genetic, the disease is believed to initiate before birth, but symptoms generally do not reveal themselves until well into adulthood.

Although ADPKD primarily affects the kidney, its pathology will spread to other organs. "Intracranial aneurysms (ICA) are a serious concern in ADPKD patients," says CiRA Professor Kenji Osafune, but not all patients will develop ICA. To understand which patients are at risk, the Osafune lab prepared iPS cells from skin cells of several ADPKD patients, some with ICA and others without, to search for molecular markers indicating higher risk. The iPS cells were then differentiated into different cell types of the vasculature and observed. "We searched for genes that had different expression levels in the two groups," said Osafune, "and found MMP1." The team then retroactively looked at the expression levels of MMP1 in hundreds of ADPKD patients and after some statistical analysis found that MMP1 expression could indeed be used as a risk factor for ICA complication.

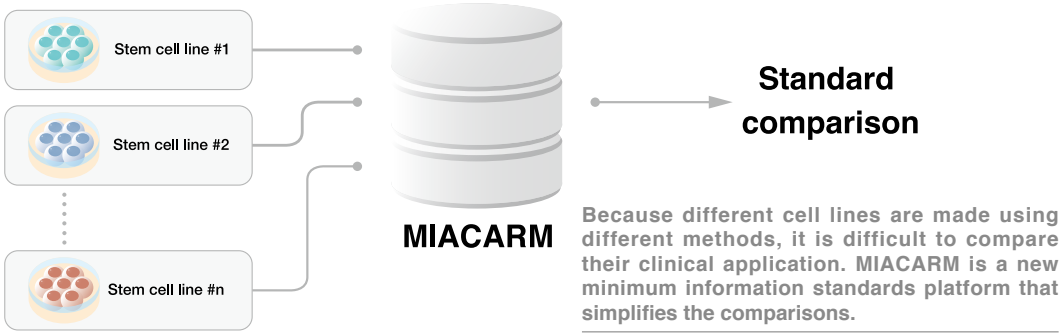
While ADPKD is a familial disease, not all patients sharing the same mutation have the same risk for ICA. To Osafune, this might indicate other genes could also contribute to ICA in ADPKD. "We are investigating other markers for ICA using our model."

Reference

Ameku T, Taura D, Sone M et al. (2016) Identification of MMP1 as a novel risk factor for intracranial aneurysms in ADPKD using iPSC models.
Scientific Reports DOI: 10.1038/srep30013

New minimum information standards for regenerative medicine

MIACARM is expected to accelerate the development of stem cell therapies



Because different cell lines are made using different methods, it is difficult to compare their clinical application. MIACARM is a new minimum information standards platform that simplifies the comparisons.

The global effort in stem cell-based regenerative medicines is expected to revolutionize patient treatment. However, the research leading to these new therapies is often based on different cell lines and cell assays. Ambiguous details about these differences could prevent reliable comparisons between methods, which could delay or stall innovation. This concern has only increased with new technologies that have expanded the information accumulated about a cell, for example, all the omics data now being collected. Accordingly, several consortia have developed minimum information standards (MIS), which describe guidelines for how to report cellular data and are the basis for relevant databases and analysis tools. Several MIS have been made for different biologics. "MIACA was made for cellular assays," explains CiRA Professor Wataru Fujibuchi, and provides a guideline for comparing different assays. However, MIACA is inadequate for regenerative medicine, which is why Fujibuchi led a team that now reports MIACARM. "MIACARM is based on MIACA," he added.

There are more than 20 cell banks, registries and databases around the world that house information on human cells for clinical research. The goal of MIACARM is to provide a standardized system that allows easy exchange of information between these sites. In essence, MIACARM reorganizes MIACA into different modules and sections in order to reduce the time and effort when surveying details of the assays, technologies and materials used to build the lines. MIACARM was also designed to identify essential items that should be available in all banks for proper regulatory compliance in the manufacturing of regenerative medicines. These include details like the stem cell ID and agencies involved in the accreditation, which surprisingly are missing in many cases.

Fujibuchi is eager to use MIACARM to consolidate data from different banks. "The lack of standards for cell preparation and cell evaluation make it difficult to decide if a treatment is safe," said Fujibuchi. MIACARM should make it easier to reproduce experiments and also have banks respond more robustly to new technologies that generate currently unavailable data.

Reference

Sakurai K, Kurtz A, Stacey G et al. (2016) First proposal of minimum information about a cellular assay for regenerative medicine (MIACARM). *Stem Cells Translational Medicine* DOI: 10.5966/sctm.2015-0393

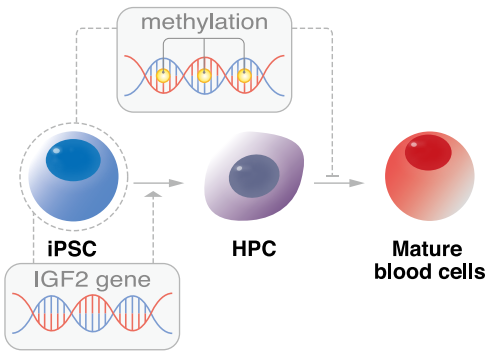
Cell origin does not affect iPS cell differentiation to blood

A new study identifies molecular markers for stable iPS cell differentiation to hematopoietic cells.

Blood describes a diverse group of cells that includes those that carry oxygen, heal wounds, and fight off infection, and the production of clinical grade blood has remained a major goal of reprogramming science. Typically, the iPS cell lines used for these experiments come from one of four types of founder cells: fibroblasts, keratinocytes, peripheral and umbilical cord blood, and dental pulp cells. Also, the method with which the transgenes are expressed to produce the iPS cell lines varies, with the most common being retrovirus, episomal plasmids and Sendai virus. Whether these differences contribute to the hematopoietic lineage capacity of an iPS cell line remains contentious.

To investigate, the Yoshinori Yoshida lab examined an unprecedented number of iPS cell lines made from the above founder cells and methods. Interestingly, they found neither had a significant effect. Instead, they show the expression of certain genes and DNA methylations are better indicators of the hematopoietic lineage potential. "We found the IGF2 gene marks the beginning of reprogramming to hematopoietic cells," said Dr. Masatoshi Nishizawa, a hematologist in the Yoshida lab and first author of the new study. The researchers show that higher expression of the growth hormone IGF2, or insulin-like growth factor 2, is indicative of iPS cells initiating their conversion into hematopoietic cells. Even though IGF2 itself is not directly related to hematopoiesis, its uptake corresponded to an increase in the expression of genes that are.

While IGF2 marked the beginnings of differentiation to hematopoietic lineage, the completion of differentiation was marked by the methylation profile of the iPS cell DNA. "DNA methylation has an effect on a cell staying pluripotent or differentiating," explained Yoshida. The completion of differentiation correlated with less aberrant methylation during the reprogramming process. Blood founder cells showed a much lower propensity for aberrant methylation than did other founder cells, which could explain why in the past scientists have attributed the founder cell to the hematopoietic lineage potential.



iPSC differentiation depends on aberrant methylation and not the founder cells or reprogramming method.

These findings reveal molecular factors that can be used to evaluate the differentiation potential of different cell lines, which should expedite the progress of iPS cells to clinical use. Nishizawa expects this work to act as a basis to evaluate cell lines for the preparation of other cell types. "I think each cell type will have its own special patterns," he said.

Reference

Nishizawa M, Chonabayahsi K, Nomura M et al. (2016) Epigenetic variation between human induced pluripotent stem cell lines is an indicator of differentiation capacity. *Cell Stem Cell* DOI: 10.1002/stem.2436

New iPS cell models to study two neurodegenerative diseases

The Haruhisa Inoue lab reports iPS cells can model two different brain diseases.

For CiRA professor and neurologist Haruhisa Inoue, iPS cells have revolutionized the study of brain disease. "Before iPS cells, all our living models for neurodegenerative diseases were based on immortalized cell lines or animals like mice," he said. Now, by reprogramming patient cells to iPS cells and then differentiating them into neurons, one can watch a neurodegenerative disease develop in real time.

In its most recent publications, the Inoue lab has reported that patient iPS cells can be used to model Alexander disease and Perry syndrome. Alexander disease is challenging to study because it "causes a wide variety of clinical symptoms, including delayed development, seizure, or spasticity," said Inoue. Similar to the amyloid plaques associated with Alzheimer's disease, Alexander disease is associated with aggregates known as Rosenthal fibers within astrocytes. Perry syndrome, on the other hand, is extremely rare, with less than 100 cases reported, and is associated with a loss of neurons in the substantia nigra, the same region that is inflicted by Parkinson's disease. "Patients normally die within five years of diagnosis due to respiratory failure," Inoue said.

At the molecular level, Alexander disease is associated with mutations in glial fibrillary protein (GFAP), which are believed to cause the Rosenthal fibers. Consistently, Inoue's team found that astrocytes derived from patient iPS cells formed Rosenthal fibers, but those derived from healthy iPS cells did not. Interestingly, patient astrocytes also expressed more cell-cell interactions and inflammation compared with healthy cells, which could explain the multiple clinical symptoms and provide a drug target for the disease. "Our next step is to look for drug compounds that can change the expression," Inoue said.

The cause of Perry syndrome is mutations in another gene. "DCTN1 produces dynactin," explained Inoue. Several different types of DCTN1 mutations have been found in Perry syndrome, and all could affect the function of dynactin, which is a protein critical for cell structure and mobility. Like Alexander disease, protein aggregates of dynactin are associated with Perry syndrome, a feature the lab confirmed in its patient iPS cell model. Perry syndrome is also associated with the aggregation of another protein, TDP-43, but TDP-43 aggregates were not seen in the iPS cell model. Inoue suspects that TDP-43 could be a late marker of Perry syndrome and that the aggregation of dynactin would make a better drug target for preventing early stages of the disease.

Reference

Alexander disease
Kondo T, Funayama M, Miyake M et al. (2016) Modeling Alexander disease with patient iPSCs reveals cellular molecular pathology of astrocytes. *Acta Neuropathologica Communications* 4(1) DOI: 10.1186/s40478-016-0337-0

Perry syndrome
Mishima T, Ishikawa T, Imamura K et al. (2016) Cytoplasmic aggregates of dynactin in iPSC-derived tyrosine hydroxylase-positive neurons from a patient with Perry syndrome. *Parkinsonism & Related Disorders* DOI: 10.1016/j.parkreldis.2016.06.007

Greetings from the
Yoshiya Kawaguchi Lab

Dept. of Clinical Application

The pancreas consists of two types of glands, exocrine and endocrine, which are respectively responsible for secreting enzymes that digest food and hormones including insulin into the bloodstream. The pancreas is a popular organ of study for regenerative medicine because of the alarming increase of diabetes patients. While future diabetes treatment aims to regenerate the lost beta cells, a strategy that concentrates on endocrine tissue, we take a more comprehensive approach to this problem.

Despite their independent functions, the development of the pancreas suggests a fair amount of interplay between the endocrine and exocrine tissues. We have hypothesized that diseases seemingly affecting only one tissue could actually involve dysfunction of the other. As an example, in our latest publication, we found using mutant mice non-cell autonomous effects, where gene knockdown in exocrine cells affected insulin production in endocrine cells (see CiRA Reporter Vol.6). These results suggest that unknown secretions by the exocrine system support proper development of the endocrine system. Thus, to obtain fully-functional endocrine cells that could be used for diabetes or other pancreas therapies, we are trying to create “whole pancreas tissue” that contains both endocrine and exocrine cells, rather than making only cells from the affected tissues.

The evidence of non-cell autonomous effects also suggests a new strategy to cancer treatment, which is a major focus of the lab. Pancreatic cancer is not the most common type of cancer according to the U.S. National Institute of Cancer, but it has an extremely high mortality rate of 80%. This link (http://www.cancer.gov/types/common-cancers)

Yoshiya Kawaguchi

shows that the only other cancer to have mortality over 50% is lung cancer. It is often thought that cancer is the result of dysfunction within the diseased cell, but poor diagnostics and treatment call for a divergence from this attitude in the case of the pancreas.

Therefore, to understand how one pancreatic tissue can cause disease in the other and to innovate therapeutics, we have focused on recapitulating pancreas development. Our expectation is that by observing all stages of pancreatic development, we will uncover new chemicals like the unknown secretion above that can become the basis for new medicines to treat multiple pancreas-related diseases.

Scientists and the public disagree on human-animal chimeras

Associate Professor Yoshimi Yashiro finds large discrepancies in the tolerance for mixing human and animal cells in the embryo

The manipulation of the embryo has always been fraught with ethical concerns. Society has generally resisted modifications to human embryos, but been comparatively more lax when dealing with animal embryos. The inexorable progress of science has now brought to the forefront a major ethical dilemma regarding animal embryos that coincides with human life. Namely, how should we govern research that involves the introduction of human pluripotent stem cells into animal embryos?

Such experiments invite the opportunity to grow human cells inside animals. Optimists have argued that these experiments mean animals can be harvested for human organs, like hearts and livers. On the flip side, these experiments could also lead to animals with human, or at least human-like, brains.

Countries have responded differently. The National Institute of Health (NIH), the largest funding body in the United States for health related research, declared in 2015 that it would not fund the above type of research, although this moratorium was lifted last August. A similar change is planned at the Japanese equivalent, Agency for Medical Research and Development (AMED), which has stated it will fund "techniques to regenerate functional solid organs based on the principles of development." This policy is a shift from 2001 policy, which explicitly prohibited implanting human-animal chimeric embryos into animal uteruses. AMED has decided that Japan would risk losing talented scientists to nations with less strict guidelines. Although this policy has not officially been implemented, its passing by the end of this year is expected to push Japan to the forefront of this science.

Public opinion will undoubtedly influence just how far the new policy will go. To gauge the current opinion, bioethicist and CiRA Associate Professor Yoshimi Yashiro has published a letter in Cell Stem Cell with two other Japanese researchers. "It is crucial that government agencies make decisions with the public's consideration in mind," said Yashiro. The three assembled the opinions of about 5000 individuals from the general public in Japan and compared them with those from members of the Japanese Society for Regenerative Medicine (JSRM). The authors found that the public was much more opposed to chimeric animals with human cells than JSRM members, but the opinions showed close agreement with research for regenerative medicine. "We found that the public has a strong aversion to research that involves mixing human and animal stem cells."

Yashiro worries that the divergence could create an antagonistic relationship between scientists and the public, since the latter may conclude that scientists are operating with little thought about the implications of their work. "Scientists should explain why these studies are necessary and safe," he said.

Reference

Inoue Y, Shineha R, and Yashiro Y (2016) Current Public Support for Human-Animal Chimera Research in Japan is Limited, Despite High Levels of Scientific Approval. *Cell Stem Cell* 19(2): 152-153.

CiRA publishes a book on iPS cells

In 2015, the publishing company PHP Institute, Inc., proposed to CiRA the idea of a book for the Japanese public that describes iPS cell research. “At the time we were planning a study on how overseas research institutes support their own researches including communications between scientists and citizens. In addition, as we had written a introductory book on iPS cells several years ago and many Japanese media cover iPS cell research in Japan, we thought it would be beneficial to give information about overseas iPS cell research progress as well as how they are supported this time,” said CiRA science communicator Ayaka Nakauchi. In time for the 10th anniversary of iPS cells, CiRA and PHP published a book on recent iPS cell research and science communication overseas, “How iPS cells would change medical treatments.” The book was written by Nakauchi and her colleague, Hiroyuki Wadahama, both members of the International Public Communications Office (IPCO) at CiRA. Along with providing an explainer about iPS cells and their potential in medical application, Nakauchi visited several institutes from around the world, including the United States, the United Kingdom, Sweden and Singapore. The book went on sale July 16 (Japanese only).

Hiroyuki Wadahama (left) and Ayaka Nakauchi with their new book

Teaching children iPS cells

The IPCO this year has released several new products to educate children and their families about iPS cells. On July 21 and 22, the IPCO held a workshop at Roppongi Hills in Tokyo designed to teach children about iPS cells. The elementary and junior high school students were invited to make and play a board game that taught them the concept of reprogramming and how iPS cells can be differentiated into various types of cells. Similarly, from July 31 to August 2, the IPCO set up a booth at Expo City, a shopping mall in Osaka Prefecture. Several hundreds of people visited and got to play with some of the IPCO’s most recent material, including iPS Master, an application for iPad that is intended to demonstrate how Professor Yamanaka and his lab members discovered the four reprogramming factors that led to the creation of iPS cells, as well as board games and card games that teach about cell reprogramming and differentiation. “We are always thinking of new ways to educate the public,” said IPCO manager Akemi Nakamura.

Children making the iPS cell board game.

CiRA Retreat

CiRA had its annual retreat on July 28-29 on Awaji Island, about four hours west of Kyoto. Although all CiRA members are based on the Kyoto University campus and CiRA has weekly internal seminars that all members attend, the retreat serves as the best opportunity for colleagues to interact and advance collaborative research.

No CiRA professors were given time to speak at the retreat. Instead, selected students and postdocs had 20 minutes each to present their research. Three guest speakers highlighted the event with one hour talks. Professor Fred Gage of the University of California San Diego and the Salk Institute for Biological Studies talked about his work on mitochondria, including a new paradigm for disease modeling. Professor Masashi Yanagisawa of the International Institute for Integrative Sleep Medicine, the University of Tsukuba and whom CiRA Director Shinya Yamanaka introduced as one of his role models in science spoke about sleep, including his work on orexin and gene analysis to elucidate the molecular mechanism that explains the onset of sleep. Finally, Professor Eric Olson of the University of Texas Southwestern spoke about RNA in heart development. The retreat also included a poster session in which groups of eight explained their own work to other group members the first half followed an open session in the second half when all participants were free to view all the posters.

Along with science, the retreat is an opportunity for CiRA members to showcase their talents and strengths beyond stem cell research. At each retreat, participants are divided into groups of 10 and given a high school science project. This year's challenge was to build a self-standing tower out of nothing more than 10 sheets of newspaper in 20 minutes. The tallest tower reached almost 4 meter. Dinner is always accompanied by entertainment, and this year the JB Band and iPS Band, both constituting CiRA members, performed.

The highlight, however, was the 1st CiRA Sumo Competition. The competition had five matches including an arm wrestling match between Yamanaka and Masamitsu Sone, a member of the Yamamoto lab. Upon taking the stage, Sone proudly exclaimed, "I will beat him," but he clearly underestimated Yamanaka's bulging biceps, which nearly knocked Sone to the floor before the match even began.

Professor Hirohide Saito (right) and Dr. Cantas Alev release their anger in the Sumo Competition.

CiRA members showcase their ingenuity with newspaper.

Marathon

On the 2nd day of the retreat, Yamanaka and 25 other participants assembled at 6:30 am for a run. Among those joining were Professors Junya Toguchida and Hirohide Saito, Assistant Professor Akira Watanabe and fundraising manager Fumitaka Watanabe. These four along with Yamanaka himself and other CiRA members will take part in the Osaka Marathon in October.

You can show your support by donating to the iPS Cell Research Fund.
(http://www.cira.kyoto-u.ac.jp/e/about/fund.html)

Learn more about the Osaka Marathon.
(https://www.osaka-marathon.com/index_en.html)

A morning run by the sea.

iPS Cell Research Support Overseas

Kako Harada is a girl inspired by iPS cells who in return is inspiring iPS cell research. Born in nearby Nara only 9 years ago, she has used her passion for the piano to perform fundraisers that support the iPS Cell Research Fund at CiRA. Kako held her first fundraising recital in Japan last year, but this past summer she was invited to play at the Japan Cultural Festival in Poland as a part of a charity event.

Kako's motivation for supporting iPS cell research comes from watching her grandmother suffer from a long bout of liver cancer. "I want to help somehow and found I could by playing the piano," she said.

Approximately 150 people attended the event including the Japanese Ambassador to Poland.

Kako Harada performing at a church in Leżajsk, Poland.
(Photo courtesy of the Harada family)

Saying thanks

CiRA is always humbled by the support it gets from the public. To express its gratitude, each year CiRA hosts events to thank its donors. This past September, CiRA held events in Kyoto and Tokyo. The one in Kyoto was held at CiRA, and attendees were given the opportunity to speak directly to faculty about CiRA research. Earlier in the month, Professor Shinya Yamanaka travelled to Tokyo, where he described advances in iPS cell research .

CiRA has its largest symposium to date for the general public

Each year, CiRA holds at least one symposium for the general public to learn about iPS cells and CiRA. The most recent was July 2 and held in Kobe, about two hours west of CiRA. The event was organized in partnership with Kobe Kaisei Hospital (KKH). The symposium had three speakers, CiRA Professors Shinya Yamanaka and Noriyuki Tsumaki and KKH Director Masahiro Kurosaka.

KKH is recognized especially for its orthopedics unit, and Kurosaka along with his title at the hospital is an esteemed orthopedic surgeon and editor of several orthopedic journals. Moreover, he taught Yamanaka when the latter was an undergraduate student at the Kobe University School of Medicine.

Kurosaka's talk, which led the symposium, focused on medicines for knee pain. Tsumaki, who is also an orthopedic surgeon, talked about his research using iPS cells to treat cartilage-related diseases. Yamanaka finished the event with a more general discussion about iPS cell research, including the iPS Cell Stock Project for Regenerative Medicine.

Shinya Yamanaka (Left) and Noriyuki Tsumaki at the symposium

The event brought over 1,400 people in attendance, the largest yet to attend a CiRA symposium. Hiroyuki Wadahama, who organized the symposium from the CiRA side, said, "We were very glad to see more than one thousand attendees. The symposia are very popular."

Celebrating Dolly

This year marks the 10th anniversary since the first report of iPS cells. It also marks the 20th anniversary of another milestone in cell reprogramming – Dolly the Sheep, arguably the world's most famous farm animal. The Roslin Institute at the University of Edinburgh, where Dolly was born, held two symposia in celebration, one for scientists and one for the general public, on Sept. 1 and 2. Although Sir Jon Gurdon, who shared the Nobel Prize with Shinya Yamanaka in 2012 proved animal cloning is possible in 1962, Dolly was the first mammal to be cloned, marking a great leap in the field of cell reprogramming. Sir Ian Wilmut, who headed the Dolly project, was the main speaker at both events. Also speaking was Yamanaka, who was delighted to receive the invitation. "Dolly was a very important discovery for my research," said Yamanaka, who added that he doubts iPS cells could have been discovered without Dolly.

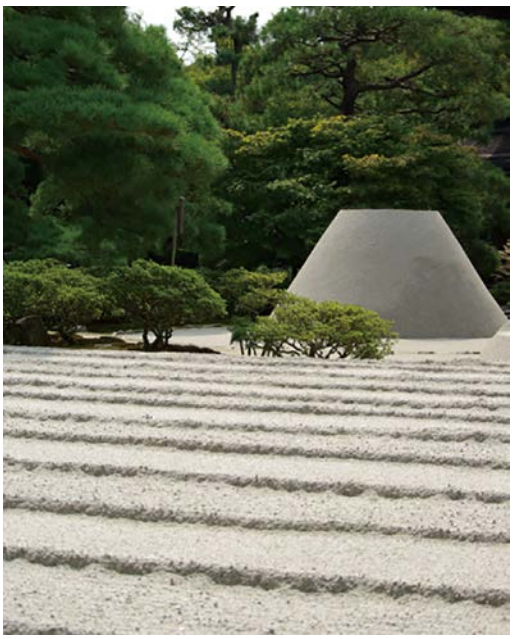
Shinya Yamanaka at the celebration

The Temples and Shrines of Kyoto

Ginkaku-ji

Ensconced at the bottom of the mountains that mark the eastern limits of Kyoto City, Ginkaku-ji was originally designed in the 15th century to give its founding Shogun a place of solitude, mostly to ignore the turmoil of the city according to several sources. Evidence of that solitude still remains, as only two main roads lead to the temple. One comes directly from Kyoto University and is a rambunctious street from which many of the tourists come travel. The other is Philosopher's Walk, which as its name suggests, is a tranquil path about 2 km that follows the foot of the mountains and passes other modest temples. The walk glows pink during the cherry blossom season, thus attracting an extraordinarily number of visitors to what already is a popular destination. On a lucky day, visitors of Philosopher's Walk will see residents preparing floats and other craft for local festivals. Esthetically, the actual temple building is less impressive than that of other temples and shrines in the city, but it compensates with its natural surroundings and gardens.

Tōgu-dō



Kogetsudai, Ginkaku-ji
Images: Robert Milewski

New CiRA webpage

2016 marks the 10th anniversary of the first iPS cell paper. To celebrate, CiRA has opened a new website that shares the history of cell reprogramming and also provides short videos of CiRA faculty describing their reaction to this monumental discovery.

(http://www.cira.kyoto-u.ac.jp/10th/e/)

They come to see trees.

Have they never seen red leaves?

People everywhere.

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